REMARKS

Reconsideration and continuing examination of the above-identified application is respectfully requested in view of the amendments above and the discussion that follows.

Claims 79-97 and 110-115 are in the case and are before the Examiner.

I. The Action

A. Rejection Under 35 USC §112, First Paragraph

Withdrawal of the previous rejection under 35 USC §112, first Paragraph is noted with appreciation.

B. Rejections Under 35 USC §103(a)

(1) Ireland In View of Zlotnick
(2) Zlotnick in view of Pumpens
(3) Thornton in view of Zlotnick

All of the presently pending claims were again rejected as allegedly obvious from one or more of the above combinations of teachings. Each of these rejections suffers from the same hindsight reconstruction fault, and is respectfully traversed.

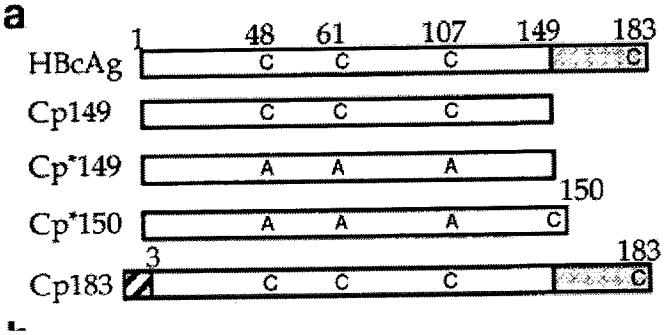
As held and recited by the CCPA,

> "it is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other

> parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art." [*In re Wesslau*, 147 USPQ 391, 393 (CCPA 1965); see also *In re Mercer*, 185 USPQ 774, 778 (CCPA 1975).]

It is again submitted that the Action has done just that, picked and chosen only so much as would support a given position and then excluded those parts of the relied-on disclosures that did not fit its preconceived notions. Because of the continued commonality of hindsight reconstruction error in the bases for rejection, the rejections will be dealt with together after a brief review of the teachings of each document.

The Action asserts in Paragraph 8 that because Zlotnick has an N-terminal Cys residue, that teaching provides a structural limitation of the claims in regard to a combination with Ireland. The Action and Paragraph 8 continuously refuse to recognize that the truncated Zlotnick construct that has a C-terminal Cys has no internal Cys residues. It was those three Ala for Cys replacements that are not conservative. On the other hand, the only truncated construct that contained internal Cys residues had no C-terminal Cys. A copy of Zlotnick's Fig. 1a is shown below.



Ireland taught insertion of a peptide sequence from the inhibin molecule into the HBc molecule at the C-terminal position of a truncated HBc whose C-terminal final HBc residue is residue 144 (a non-cysteine), and also within the sequence of the full-length core polypeptide at position 78. Thus, the former Ireland chimer contained no C-terminal Cys, whereas the latter Ireland chimer contained a Cys at position 183 or 185, depending on which strain of HBV was used. Neither insertion nor resulting chimer is useful in leading to the claimed invention.

Thus, when combined with Zlotnick, one must C-terminally truncate the construct used by Ireland and if one put Ireland's peptide into Zlotnick's Cp*150 construct there would be non-conservative substitutions at positions 48, 61 and 107. A similar result occurs when the Pumpens and Zlotnick teachings are combined.

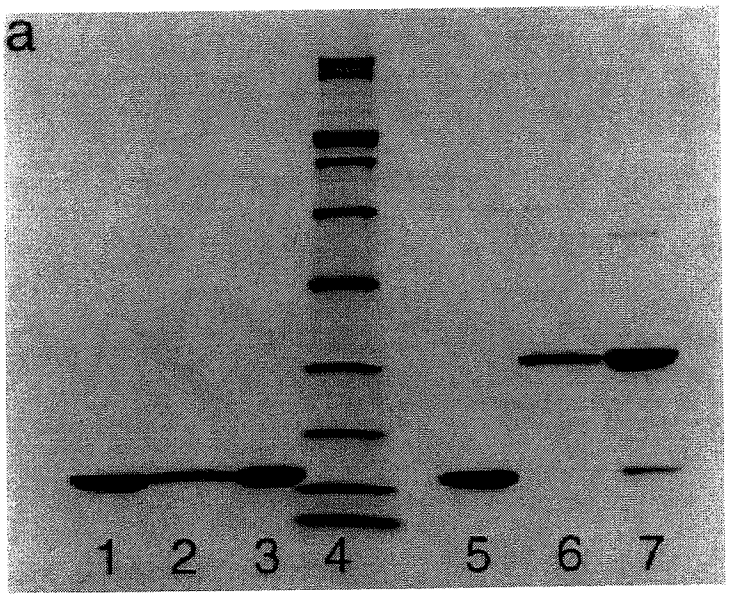
When one studies Thornton, one finds that the inserted sequence can be placed almost anywhere in the HBc sequence. It is submitted that that disclosure is so diffuse as to be of no use to any worker without undue experimentation as to what would work and form particles. Even if one were to combine the teachings of Thornton and Zlotnick, the same result would occur as happened with the combinations of Zlotnick and either Pumpens or Ireland; i.e., a construct not within those encompassed by the claims.

The Action has placed great emphasis on the results reported by Zlotnick regarding the effect of the C-terminal cysteine residue present in the so-called Cp*150 construct and how those effects would suggest the claimed invention to a worker of ordinary skill in the art. However, the premise that

Zlotnick teaches that C-terminal cysteine can stabilize an HBc chimer particle as recited in the claims here cannot be agreed with. This premise is inconsistent with the statements and data provided therein by Zlotnick.

Zlotnick explicitly states: "[p]urified Cp*149 and Cp*150 assemble into capsids under the same conditions as other constructs, with or without DTT. These capsids were *indistinguishable* (emphasis added) by negative staining electron microscopy and sedimentation on sucrose gradients." (See page 9598, column 1, paragraph 1, Results and Discussion section.) As a second example, Zlotnick reports: "[a]t a resolution of ≈20Å, the outer surface of the Au11-labeled [monomaleimidyl-undecagold-labeled] Cp*150 capsid is *indistinguishable* (emphasis added) from those of unlabeled Cp147 and Cp183 capsids, (cf. Fig. 4 top)." (See page 9558, column 2, paragraph 1.) These facts would lead one skilled in the art to conclude that C-terminal cysteines are not important for HBcΔ capsid formation or stability.

Examination of Fig. 2a of Zlotnick (below) shows that the greatest mass there shown for reduced and non-reduced protein corresponded to a little more than that of the 31 kDa molecular weight standard. That molecular weight is about that expected for a dimer of two strands of 150 residues (150 residues X 109 average molecular wt/residue = 16.35 kDa). The reported results in that figure therefore relate only to dimers and monomers.



The present claims recite stability of the particles assembled from those monomers and dimers. As such, a disclosure concerning the stability or lack thereof of dimers or monomers neither teaches nor suggests anything of relevance to the claimed subject matter whether taken alone or with any other disclosure. Still further, it is not logical to conclude that large molecular weight, structurally folded, dense capsid molecules that contain 90 or 120 dimers would behave identically to their constituent dimers. One of skill in the art would recognize this.

Furthermore, nothing in Zlotnick has shown that capsids behave like dimers. In fact, the contrary is true. For example, Zlotnick states: "[a]ssembled capsids of reduced Cp*150 did not react with Au11. Apparently, the C-terminal cysteine is inaccessible. Accordingly, Cp*150 was labeled with Au11 at neutral pH and low ionic strength, where the sample is mainly free dimers." (See page 9558, column 1, paragraph 3.) Therefore, it is improper to conclude that capsids behave like

dimers as was done in the Action in reference to Figure 2 of Zlotnick.

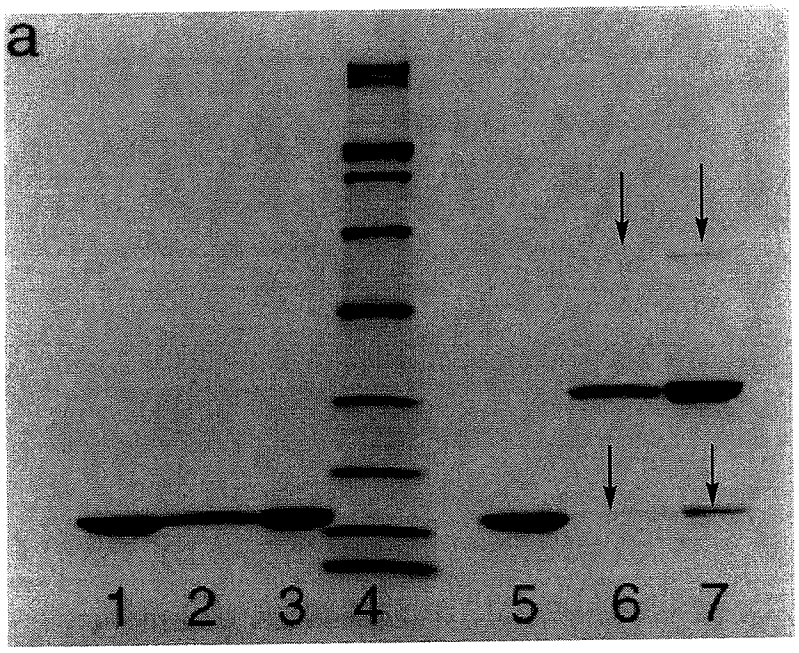
Importantly, it further appears that in Zlotnick's Figure 2, two crucial controls are lacking. One missing control is a sequence of the truncated 150-mer with the C-terminal cysteine replaced by an alternative amino acid. Without this crucial control, one of skill in the art could reasonably conclude that the polymerization of Cp*150 was due to the increase in length of the peptide from 149 amino acids to 150 amino acids. This is a perfectly plausible conclusion. In fact, this is the *only* difference between Cp*149 and Cp*150. Zlotnick did not show otherwise.

This conclusion is even more plausible given the fact the addition of gold at the C-terminus also promotes aggregation. Zlotnick states: "[t]hus it appears that modification of Cp*150 with Au11 promotes polymerization. The Au11 has a single reactive maleimide group and cannot crosslink proteins." (See page 9558, column 1, paragraph 3.) Thus, length rather than disulfide bond formation led to polymerization. Also, Zlotnick states: "[o]ther observations imply that the C termini also may influence assembly in more subtle ways. For instance binding Au11 to Cp*150 induces assembly, though Au11 cannot crosslink subunits, nor, because of its organic shell, coordinate C-terminal cysteines." (See page 9540, column 2, paragraph 1.)

In that same paragraph, while relating to the gold-labeled mutants, Zlotnick further goes on to hypothesize that changes in the molecular surface near the C-terminus may stimulate the assembly process. Therefore, one of skill in the art would reasonably conclude from these statements that

Zlotnick teaches that dimer formation is induced by merely increasing length of the mutant protein, since aggregation also occurs in the absence of free cysteine at the C-terminus of the protein.

Further still, upon careful scrutiny of Zlotnick's gel of Fig. 2a, below, one can see in the studies run under non-reducing conditions shown in lanes 6 and 7 (note the arrows provided by the undersigned) that there is a band at the lower edge of the gel near the spot of 14.4 kDa standard that clearly indicates that some of the Cp*150 sample has either failed to associate into a dimer or has readily dissociated at pH 9.5. There is a similar band at pH 7.5. A recently obtained sharper, color copy of the Zlotnick paper is attached for the Examiner's convenience to better see those disclosures.



The gel of Zlotnick's Fig. 2a (above) also shows two protein bands at a molecular mass between 45 kDa and 66 kDa that are also delineated by counsel's arrows. No evidence of the presence of capsids is shown in the gel. However, the those heavier bands indicate some sort of instability.

The enhanced stability claimed here does not relate to the equilibrium of monomeric and polymeric (dimeric) forms in the particles themselves as is disclosed by Zlotnick. As such, it is of little moment to the present invention whether "disulfide bond formation by Cp*150 can promote capsid assembly" because capsid assembly does not equate to nor suggest protein stability from degradation on dissolution of chimer protein particles in aqueous buffer at 37° C for about two weeks. In addition, the quote above from page 9558 said that Cp*149 and Cp*150 assemble into capsids under the same conditions as other constructs, with or without DTT, and that those capsids were indistinguishable.

The Action asserted that the amendment to the independent claims "did not constitute a structural or functional limitation to the alleged HBc chimer. . ." (paragraphs 12 and 13) as that amendment related to a method of measurement. It is submitted that the recited assay technique along with the previous recitation of enhanced stability together constitute a functional limitation by reciting how one determines enhanced stability of the formed particles.

The results shown in Zlotnick's Fig. 2a indicate that the protein of the cysteine-containing chimers polymerized to dimers at pH 9.5 were less pure than that polymerized at pH 7.5. It is submitted that Zlotnick has no teaching related particle

stability in the form of protein degradation, as compared to dimer stability. The claims here were amended to clarify that the stability recited relates to the particles, and as such constitute a functional limitation. It is thus again submitted that this basis for rejection should be withdrawn.

The present Action has reiterated the rejections from the previous Actions, has again failed to properly embrace the importance of the teachings of workers at least ordinary skill in this art, Ulrich et al., Newman et al. and Lachmann et al., and asserted that work to be irrelevant to this application. Those researchers worked in this field, knew of, understood and cited Zlotnick's work, and then disregarded it for dealing with particle stability. Disregarding those real workers of at least ordinary skill, the Actions have grasped and held on to the straw of an imaginary combination of the Pumpens and Zlotnick teachings that the real workers rejected. This failure to appreciate the true teachings of the art to forward-looking workers of ordinary skill is inappropriate and should be withdrawn. The previously filed arguments are hereby incorporated by reference into this reply.

The Action concluded this part of the rejection in Paragraph 15 by asserting:

> [a]pplicant has not explicitly taught any specific structures of the alleged HBc chimer that are different from those of the prior art, and any evidence to show how such specific structures of the alleged HBc chimer result in the alleged stability of the claimed HBcchimer.

That statement cannot be agreed with.

The application notes throughout that the "one to ten cysteine residues toward the C-terminus [C-terminal cysteine residue(s)]. . . within about 30 residues from the C-terminus of the chimer" that also contains the remaining internal three cysteines and an otherwise destabilizing inserted sequence at one or more of three specifically defined locations results in a chimer particle that is more stable than an chimer particle "formed from an otherwise identical HBc chimer molecule that lacks said C-terminal cysteine residue or in which a C-terminal cysteine residue present in the chimer molecule is replaced by another residue." That language has been present in the claims from the first filing.

The previous response provided further copies of Figs. 3, 4 and 8 that provided evidence of particle stability. The Examiner's attention is also invited to Examples 22 and 23 of the specification that specifically relate to stability studies on assembled particles. It should also be noted that the particles containing an added C-terminal Cys residue exhibited unexpectedly greater immunogenicity that did similar particles lacking that C-terminal Cys. This can be seen from the data in Table 20.

II. Summary

Each of the bases for rejection has been dealt with and overcome or otherwise made moot.

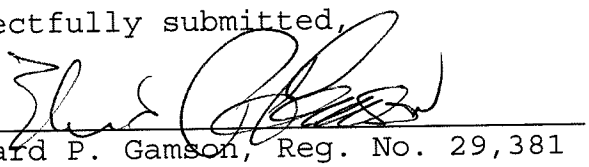
It is therefore believed that this application is in condition for allowance of all of the pending claims. An early notice to that effect is earnestly solicited.

A fee for the filing of the Actions from the other application is enclosed. No further fee or petition is believed

to be necessary. However, should any further fee be needed, please charge our Deposit Account No. 23-0920, and deem this paper to be the required petition.

The Examiner is requested to phone the undersigned should any questions arise that can be dealt with over the phone to expedite this prosecution.

Respectfully submitted,

By 
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Enclosures

Petition and Fee
RCE and Fee
Color copy of Zlotnick paper